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### Authors

French, Aimee  
Balfe, David  
Mirocha, James M  
et al.

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# The inspiratory capacity/total lung capacity ratio as a predictor of survival in an emphysematous phenotype of chronic obstructive pulmonary disease

Aimee French  
David Balfe  
James M Mirocha  
Jeremy A Falk  
Zab Mosenifar

Cedars-Sinai Medical Center, Division  
of Pulmonary and Critical Care  
Medicine, Los Angeles, CA, USA

**Background:** Forced expiratory volume in 1 second ( $FEV_1$ ) grades severity of COPD and predicts survival. We hypothesize that the inspiratory capacity/total lung capacity (IC/TLC) ratio, a sensitive measure of static lung hyperinflation, may have a significant association with survival in an emphysematous phenotype of COPD.

**Objectives:** To access the association between IC/TLC and survival in an emphysematous phenotype of COPD.

**Methods:** We performed a retrospective analysis of a large pulmonary function (PF) database with 39,050 entries, from April 1978 to October 2009. Emphysematous COPD was defined as reduced  $FEV_1$ /forced vital capacity (FVC), increased TLC, and reduced diffusing capacity of the lungs for carbon monoxide (DLCO; beyond 95% confidence intervals [CIs]). We evaluated the association between survival in emphysematous COPD patients and the IC/TLC ratio evaluated both as dichotomous ( $\leq 25\%$  vs  $> 25\%$ ) and continuous predictors. Five hundred and ninety-six patients had reported death dates.

**Results:** Univariate analysis revealed that  $IC/TLC \leq 25\%$  was a significant predictor of death (hazard ratio [HR]: 2.39,  $P < 0.0001$ ). Median survivals were respectively 4.3 (95% CI: 3.8–4.9) and 11.9 years (95% CI: 10.3–13.2). Multivariable analysis revealed age (HR: 1.19, 95% CI: 1.14–1.24), female sex (HR: 0.69, 95% CI: 0.60–0.83), and  $IC/TLC \leq 25\%$  (HR: 1.69, 95% CI: 1.34–2.13) were related to the risk of death. Univariate analysis showed that continuous IC/TLC was associated with death, with an HR of 1.66 (95% CI: 1.52–1.81) for a 10% decrease in IC/TLC.

**Conclusion:** Adjusting for age and sex,  $IC/TLC \leq 25\%$  is related to increased risk of death, and IC/TLC as a continuum, is a significant predictor of mortality in emphysematous COPD patients.

**Keywords:** emphysema, pulmonary function testing, mortality

## Introduction

COPD represents an important public health challenge that is both treatable and preventable.<sup>1</sup> Currently, COPD is the fourth leading cause of death worldwide and is expected to be the third leading cause of death by 2020.<sup>2</sup> Despite efforts from the medical community, the Centers for Disease Control (CDC) reports that smoking rates in the US have only slightly declined since 1997 from 24.7% to 20.8%.<sup>3</sup> With COPD prevalence increasing, accurate assessments of COPD comorbidities and mortality are needed.<sup>4–25</sup> COPD results from the interplay between genetic susceptibility and exposure to environmental stimuli.<sup>26</sup>

Correspondence: David Balfe  
Cedars-Sinai Medical Center, Division  
of Pulmonary and Critical Care Medicine,  
8700 Beverly Blvd, Suite 6732, Los  
Angeles, CA, USA  
Tel +1 310 423 1835  
Fax +1 310 423 0129  
Email balfed@csmc.edu

In 1977, Fletcher and Peto described the natural history of COPD, including its relationship with smoking and decline in forced expiratory volume in 1 second ( $FEV_1$ ).<sup>27</sup> Since that time, COPD has been characterized as a poorly reversible airflow limitation, most often defined by  $FEV_1$ .<sup>8</sup> Historically, the reduction in  $FEV_1$  has been used to define the severity of COPD and frequently cited as an important predictor of mortality.<sup>24</sup> Additionally,  $FEV_1$  is frequently targeted as a clinical endpoint in COPD clinical trials.<sup>28–34</sup> Other clinical measurements such as inspiratory capacity (IC), 6-minute walk test (6MWT), the BODE index (body mass index, airflow obstruction, dyspnea, and exercise), and dyspnea questionnaires may have stronger associations with mortality than  $FEV_1$ .<sup>7,12–16,19,24,35–39</sup>

Several publications have focused on the use of the IC/total lung capacity (TLC) ratio, a measure of static lung hyperinflation, which has been shown to be strongly associated with exercise-associated dynamic hyperinflation as well as exercise tolerance.<sup>4,8,38,40</sup> Additionally, studies evaluating the use of resting IC have also demonstrated a strong association between IC and functional exercise limitation in COPD patients.<sup>41,42</sup> In 2004, Casanova et al evaluated the role of the IC/TLC ratio, in conjunction with the BODE index and  $FEV_1$ .<sup>7</sup> Their cohort consisted of 689 patients (95% male) with 183 deaths (178 males and five females) with a median follow-up less than 3 years; their results suggested that when compared to  $FEV_1$  and the BODE index, an IC/TLC ratio of  $\leq 25\%$  offered the best combined sensitivity and specificity for predicting all-cause mortality in COPD patients.<sup>7</sup> We hypothesize that the IC/TLC ratio is associated with risk of death, when used to evaluate a large cohort over an extended period of follow-up and could be a useful clinical tool in assessing patients with an emphysematous phenotype of COPD.

## Methods

We performed a retrospective analysis of a large pulmonary function (PF) database, consisting of 39,050 entries, from our institution, which encompasses a broad patient population of inpatients and outpatients from April 1978 to October 2009. Cedars-Sinai Medical Center Institutional Review Board approval (Pro-00012916) was obtained for the study. We evaluated the IC/TLC ratio and its association with survival. All available studies were evaluated, which consisted of 39,050 entries. We defined COPD patients with an emphysematous phenotype as those with a reduced  $FEV_1/FVC$  ratio, increased TLC, and reduced diffusing capacity of the lungs for carbon monoxide (DLCO; all beyond 95% confidence

intervals) using established normal values.<sup>42–44</sup> If the same patient had multiple PF studies, only the first recorded PF was included in the study analysis. Lastly, patients were excluded if they were under the age of 18 years. Using the Social Security National Death Index (SSNDI), we established absolute dates of death. If the subject did not have a reported date of death in the SSNDI, they were assumed to be alive 8 weeks prior to the date that the SSNDI was queried. Univariate analysis was completed to evaluate the relationship between IC/TLC ratio and survival. Additionally, disease severity was graded using the  $FEV_1$  as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.<sup>46</sup> Body mass index (BMI) was treated as ordered categories (BMI:  $<20$  low,  $\geq 20$ – $25$  normal,  $\geq 25$  overweight/obese). As done previously in the NETT trial, DLCO was treated as a binary variable, with a cut-off of  $<22\%$ .<sup>47</sup> Finally, multivariable analysis assessing the associations of age, sex,  $FEV_1$ , DLCO, IC, and BMI in conjunction with the IC/TLC ratio was performed. All studies were performed on equipment manufactured by the SensorMedics Corporation. IC measurements were made during the enhanced spirometry section with deep inspiration occurring after a period of stable tidal breathing; all tests were performed according to the American Thoracic Society (ATS) criteria. Single-breath DLCO measurements were made according to ATS criteria with a 10-second breath-hold; correction for hemoglobin was not performed. TLC was measured using plethysmography as per ATS criteria. Forced expiratory spirometry was obtained pre- and post-spirometry; plethysmography was obtained post-bronchodilator.

Numerical variables were summarized by mean and standard deviation or median and interquartile range (IQR), as appropriate, depending on the normality of the distribution. Group differences on numerical variables were assessed by Student's *t*-tests (normality was satisfied) or the Wilcoxon rank-sum test (normality was violated). Categorical variables were summarized by frequency and percentage and compared across groups by the chi-square test or Fisher's exact test, as appropriate. Survival was estimated by the Kaplan–Meier method. Group differences in survival were assessed by the log-rank test. Survival differences across ordinal explanatory variables were assessed by trend tests. Factors associated with the risk of death were assessed by multivariable Cox proportional hazards models. The proportional hazards assumption was assessed by the supremum test and by analysis of Schoenfeld residuals. Hazard ratios (HRs) and their associated 95% CIs were reported where possible. Two-sided *P*-values were reported for all comparisons.

Statistical calculations were made using SAS software (v9.1.3; SAS Institute Inc., Cary, NC, USA).

## Results

Our database consisted of 39,050 PF tests; 14,322 were excluded because they had no DLCO recorded. The remaining 24,728 PFs that were excluded, either did not meet criteria for obstruction or were repeat PF tests. Nine-hundred and eighty-four patient PFs meeting criteria were analyzed (Figure 1). The study cohort consisted of 436 females and 548 males. Five hundred and ninety-six subjects had reported dates of death.

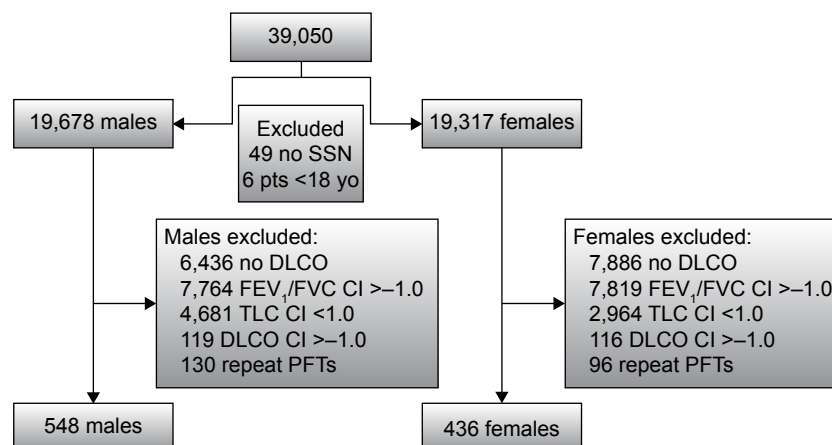
Baseline characteristics are reported in Table 1. As displayed in Table 1, there were notable differences between the 'dead' and 'alive' groups. 'Alive' patients were younger, had a higher BMI, a higher FEV<sub>1</sub>/FVC ratio, and higher predicted FEV<sub>1</sub> with a larger percentage being defined as having mild COPD. In regards to lung volumes, 'alive' patients had a slightly lower TLC, higher DLCO, higher IC, and had better IC/TLC ratios than patients in the 'dead' group.

The potential predictors of all-cause mortality are shown in Tables 2 and 3.

Univariate analysis revealed that IC/TLC, % DLCO, sex, age, BMI, IC, and FEV<sub>1</sub> were all significantly associated with survival (Table 2; Figures 2, 3, and 4). Using an IC/TLC  $\leq 25\%$  compared to IC/TLC  $> 25\%$ , there was a significant decrease in survival (HR: 2.39, 95% CI: 2.03–2.82,  $P < 0.0001$ ). The median survival was 4.3 years for IC/TLC  $\leq 25\%$  (95% CI: 3.8–4.9 years) versus 11.9 years for IC/TLC  $> 25\%$  (95% CI: 10.3–13.2 years). Five-year survival for IC/TLC  $\leq 25\%$  versus IC/TLC  $> 25\%$  was 43.9% (95% CI: 38.7%–49.0%) versus 73.4% (95% CI: 69.6%–76.9%),

respectively. Additionally, a DLCO  $< 22\%$  versus a DLCO  $\geq 22\%$  was associated with an increased risk of death (HR: 2.08, 95% CI: 1.68–2.57,  $P < 0.0001$ ). The median survival for a DLCO  $< 22\%$  was 3.77 years (95% CI: 2.94–4.60 years). Females had reduced risk of death (HR: 0.78, 95% CI: 0.66–0.92,  $P = 0.003$ ). Median survival for females was 8.7 years (95% CI: 7.7–10.1 years) versus 7.0 years for males (95% CI: 5.7–8.2 years). A 5-year increase in age revealed a 23% increased risk of death (HR: 1.23, 95% CI: 1.18–1.28,  $P < 0.0001$ ). Compared to a normal BMI ( $\geq 20$  to  $< 25$ , the reference level), patients with a BMI  $< 20$  were at greater risk of death (HR: 1.22, 95% CI: 0.99–1.51,  $P = 0.068$ ). However, a BMI  $\geq 25$  appeared to be protective (HR: 0.81, 95% CI: 0.67–0.97,  $P = 0.022$ ). An IC  $\geq 80\%$  was associated with a reduced risk of death (HR: 0.48, 95% CI: 0.41–0.57,  $P < 0.0001$ ). Lastly, FEV<sub>1</sub> was evaluated using moderate COPD disease, as defined by GOLD criteria, as the reference group: patients with mild COPD were less likely to die (HR: 0.48, 95% CI: 0.35–0.65,  $P < 0.001$ ); however, both severe (HR: 1.38, 95% CI: 1.11–1.70,  $P = 0.003$ ) and very severe COPD (HR: 1.81, 95% CI: 1.46–2.23,  $P < 0.0001$ ) patients were at increased risk of death.

In addition, a multivariable analysis was performed to assess the associations of age, sex, FEV<sub>1</sub>, % DLCO, IC, and BMI in conjunction with the IC/TLC ratio. Analysis revealed that age (5-year increase in age), sex, IC/TLC  $\leq 25\%$ , FEV<sub>1</sub>, BMI  $< 20$ , and DLCO  $< 22\%$  remained statistically significant factors associated with the risk of death (Table 3). Patients with a DLCO  $< 22\%$  had an increased risk of death when compared to patients with a DLCO  $\geq 22\%$  (HR: 1.28, 95% CI: 1.01–1.61,  $P = 0.043$ ) (Figure 5). Compared to a normal BMI ( $\geq 20$  to  $< 25$ , the reference level), patients with



**Figure 1** Patient flow chart.

**Abbreviations:** CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; PFTs, pulmonary function test; pts, patients; SSN, Social Security number; TLC, total lung capacity.

**Table 1** Baseline characteristics and univariate analysis

Variable	All patients (N=984)	Alive (N=388)	Dead (N=596)	P-value
Female, n (%)	436 (44.3)	191 (49.2)	245 (41.1)	0.013
Age, mean years $\pm$ SD	62.7 $\pm$ 12.1	58.2 $\pm$ 13.3	65.6 $\pm$ 10.3	<0.0001
BMI, mean $\pm$ SD	24.2 $\pm$ 4.6	25.0 $\pm$ 4.5	23.7 $\pm$ 4.6	<0.0001
FEV <sub>1</sub> /FVC%, mean $\pm$ SD	46.8 $\pm$ 13.4	51.8 $\pm$ 13.7	43.5 $\pm$ 12.2	<0.0001
FEV <sub>1</sub> predicted %, mean $\pm$ SD	50.2 $\pm$ 25.49	57.9 $\pm$ 26.79	45.1 $\pm$ 23.29	<0.0001
Stage (GOLD)				<0.0001
Mild, $\geq$ 80% of predicted, n (%)	162 (16.5)	106 (27.3)	56 (9.4)	
Moderate, 50%–79% of predicted, n (%)	265 (26.9)	107 (27.6)	158 (26.5)	
Severe, 30%–49% of predicted, n (%)	283 (28.8)	99 (25.5)	184 (30.9)	
Very severe, <30% of predicted, n (%)	274 (27.8)	76 (19.6)	198 (33.2)	
% TLC, mean $\pm$ SD	135.15 $\pm$ 11.12	133.7 $\pm$ 10.17	136.1 $\pm$ 11.56	0.001
% DLCO, mean $\pm$ SD	43.2 $\pm$ 17.74	49.9 $\pm$ 17.59	38.8 $\pm$ 16.43	<0.0001
DLCO <22%, n (%)	126 (12.8)	21 (5.4)	105 (17.6)	<0.0001
% IC, mean $\pm$ SD	92.0 $\pm$ 27.74	98.8 $\pm$ 26.79	87.7 $\pm$ 27.53	<0.0001
IC $\geq$ 80%, n (%)	632 (64.2)	295 (76.0)	337 (56.5)	<0.0001
BMI				<0.0001
Low, <20, n (%)	176 (17.9)	52 (13.4)	124 (20.8)	
Normal, 20 to <25, n (%)	407 (41.4)	144 (37.1)	263 (44.1)	
High $\geq$ 25, n (%)	401 (40.7)	192 (49.5)	209 (35.1)	
IC/TLC, mean % $\pm$ SD	28.7 $\pm$ 9.8	32.0 $\pm$ 10.2	26.6 $\pm$ 8.9	<0.0001
IC/TLC $\leq$ 25%, n (%)	395 (40.1)	99 (25.5)	296 (49.7)	<0.0001

**Notes:** Baseline characteristics of survivors and nonsurvivors. Subjects who died were more likely to be male, had greater airflow obstruction, an IC/TLC  $\leq$ 25%, lower BMI, and were older.

**Abbreviations:** BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; SD, standard deviation; TLC, total lung capacity.

a BMI <20 were at greater risk of death (HR: 1.22, 95% CI: 0.97–1.53,  $P=0.089$ ). In contrast, a BMI  $\geq$ 25 appeared to be protective (HR: 0.81, 95% CI: 0.67–0.97,  $P=0.022$ ) (Figure 6). Lastly, FEV<sub>1</sub> was evaluated using moderate COPD disease, as defined by GOLD criteria, as the reference group. Patients with mild COPD were less likely to die (HR: 0.66, 95% CI: 0.48–0.90,  $P=0.009$ ). Additionally, neither severe (HR: 1.01, 95% CI: 0.80–1.27,  $P=0.95$ ) nor very severe COPD (HR: 1.06, 95% CI: 0.79–1.41,  $P=0.71$ ) patients were at increased risk of death, compared to the moderate group in

the multivariate analysis. In summary, increasing age, IC/TLC  $\leq$ 25%, DLCO <22%, and a BMI <20 were associated with increased risk of death. Female sex and a higher BMI were protective.

Lastly, we completed a univariate analysis of the IC/TLC ratio as a continuous predictor of the risk of death. Over the entire range of IC/TLC (8%–63%), a 10% decrease in IC/TLC was associated with a 66% increase in the risk of death (HR: 1.66, 95% CI: 1.52–1.81,  $P<0.0001$ ). For clinical applicability, we categorized the ratio into

**Table 2** Univariate analysis

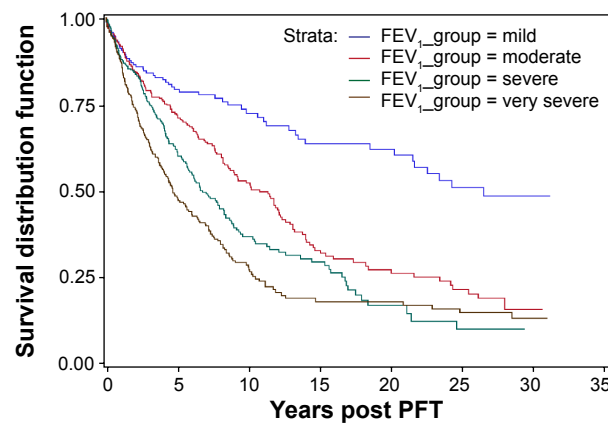
Variable	HR	95% CI	P-value
Age (5-year increase)	1.23	1.18–1.28	<0.0001
Female	0.78	0.66–0.92	0.003
IC/TLC $\leq$ 25%	2.39	2.03–2.82	<0.0001
FEV <sub>1</sub> mild vs moderate	0.48	0.35–0.65	<0.0001
FEV <sub>1</sub> severe vs moderate	1.38	1.11–1.70	0.003
FEV <sub>1</sub> very severe vs moderate	1.81	1.46–2.23	<0.0001
BMI <20 vs BMI 20 to <25	1.22	0.99–1.51	0.068
BMI $\geq$ 25 vs BMI 20 to <25	0.81	0.67–0.97	0.022
DLCO <22%	2.08	1.68–2.57	<0.0001
IC $\geq$ 80%	0.48	0.41–0.57	<0.0001

**Abbreviations:** BMI, body mass index; CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, hazard ratio; IC, inspiratory capacity; TLC, total lung capacity.

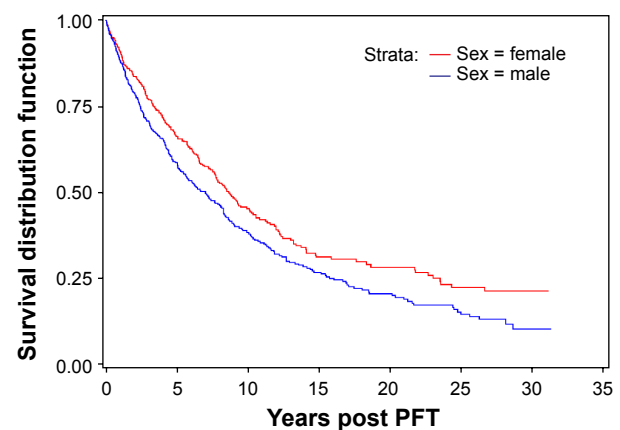
**Table 3** Multivariable analysis

Variable	HR	95% CI	P-value
Age (5-year increase)	1.19	1.14–1.24	<0.0001
Female	0.69	0.58–0.83	<0.0001
IC/TLC $\leq$ 25%	1.69	1.34–2.13	<0.0001
FEV <sub>1</sub> mild vs moderate	0.66	0.48–0.90	0.009
FEV <sub>1</sub> severe vs moderate	1.01	0.80–1.27	0.95
FEV <sub>1</sub> very severe vs moderate	1.06	0.79–1.41	0.71
BMI <20 vs BMI 20 to <25	1.22	0.97–1.53	0.089
BMI $\geq$ 25 vs BMI 20 to <25	0.81	0.67–0.97	0.022
DLCO <22%	1.28	1.01–1.61	0.043

**Abbreviations:** BMI, body mass index; CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, hazard ratio; IC, inspiratory capacity; TLC, total lung capacity.



**Figure 2** Survival by predicted  $FEV_1$  level as defined by GOLD criteria.  
**Abbreviations:**  $FEV_1$ , forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PFT, pulmonary function test.



**Figure 4** Patient survival by sex.  
**Abbreviation:** PFT, pulmonary function test.

four levels:  $IC/TLC >45\%$  (the reference level),  $>35\%$  to  $\leq 45\%$ ,  $>25\%$  to  $\leq 35\%$ , and  $\leq 25\%$  (Table 4; Figure 7). Compared to patients with  $IC/TLC >45\%$ , patients with  $IC/TLC >35\%$  to  $\leq 45\%$  were at 76% increased risk of death (HR: 1.76, 95% CI: 1.07–2.89); patients with  $IC/TLC >25\%$  to  $\leq 35\%$  were at 182% increased risk of death (HR: 2.82, 95% CI: 1.76–4.53); and patients with  $IC/TLC \leq 25\%$  were at 423% increased risk of death (HR: 5.23, 95% CI: 3.28–8.35). Median survivals (95% CI) were 4.3 (3.8–4.9) years for patients with  $IC/TLC \leq 25\%$ , 8.9 (7.7–10.5) years for patients with  $IC/TLC >25\%$  to  $\leq 35\%$ , and 14.1 (11.9–18.7) years for patients with  $IC/TLC >35\%$  to  $\leq 45\%$ . Median survival was not yet reached in patients with  $IC/TLC >45\%$  (30-year survival estimate 52.3%).

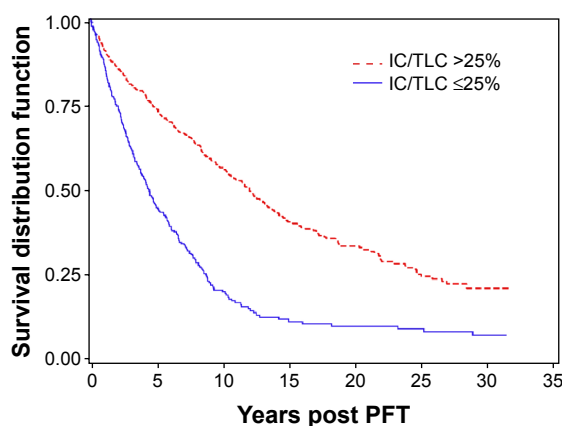
## Discussion

Using an  $IC/TLC$  ratio of  $\leq 25\%$ , a representation of static lung hyperinflation, we were able to demonstrate that the  $IC/TLC$

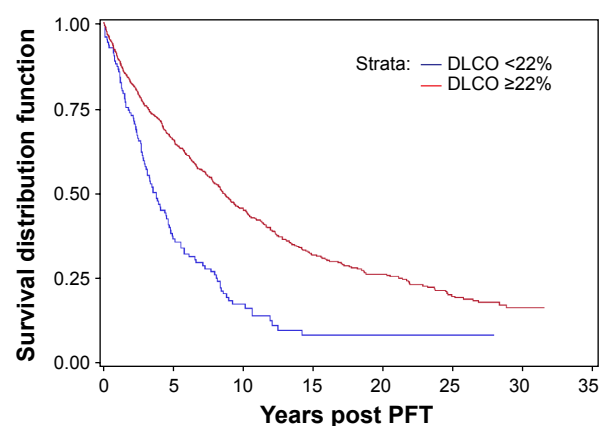
ratio correlated with risk of death in patients with an emphysematous phenotype of COPD. Patients with an  $IC/TLC$  ratio  $\leq 25\%$  had a median survival of 4.3 years versus 11.9 years for those patients with an  $IC/TLC >25\%$ . The use of the  $IC/TLC$  ratio, as a single predictor variable, in patients with COPD, will allow clinicians to better evaluate and risk-stratify patients with an emphysematous phenotype of COPD.

In the 35 years since Fletcher and Peto described the natural history of COPD, our understanding about the disease process has been an ongoing development.<sup>27</sup> Although initial studies supported  $FEV_1$  as the best predictor of COPD mortality,<sup>47</sup> more recent literature has revealed that a variety of factors are more accurate predictors of mortality than  $FEV_1$ .<sup>7,12–16,19,24,34–39</sup> Interest has been shown in the role of the vitamin D pathway in COPD, with vitamin D deficiency correlating with the risk of COPD.<sup>26</sup>

In addition to  $IC/TLC$  and  $FEV_1$ , we also examined the relationship of  $IC$ , age, BMI, DLCO, and sex (Tables 1 and 3)

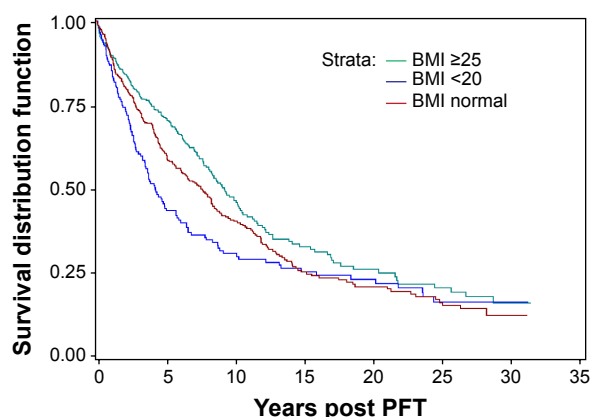


**Figure 3** Patient survival by  $IC/TLC$ .  
**Abbreviations:**  $IC$ , inspiratory capacity;  $TLC$ , total lung capacity; PFT, pulmonary function test.



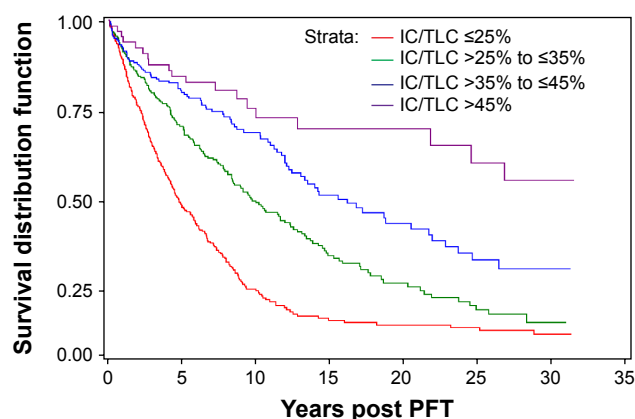
**Figure 5** Patient survival by DLCO.  
**Abbreviations:** DLCO, diffusing capacity of the lungs for carbon monoxide; PFT, pulmonary function test.





**Figure 6** Survival by BMI level.

**Abbreviations:** BMI, body mass index; PFT, pulmonary function test.



**Figure 7** Patient survived by IC/TLC level.

**Abbreviations:** IC, inspiratory capacity; TLC, total lung capacity; PFT, pulmonary function test.

and their associations with the risk of death. Specifically, our multivariable analysis demonstrated that IC alone was not a reliable predictor of mortality, contrary to what has been previously reported in a milder COPD population.<sup>24</sup> We were able to demonstrate that age and BMI were associated with risk of death but did not demonstrate as clear an association as the IC/TLC. In regards to sex, Kaplan–Meier analysis revealed that females had a survival advantage when compared directly to males with COPD. Ringbaek et al previously reported that when compared to standardized mortality rates expected in the general population, it appeared that females with COPD actually have more years of life lost than their male counterparts.<sup>21</sup> Furthermore, when examining the DLCO, we found a significant association with risk of death. However, our cohort had only 126 patients with a DLCO  $\leq 22\%$ .

Our study had a number of strengths. To our knowledge, it is the first study to evaluate mortality over 34 years of reported data in an emphysematous phenotype of COPD. Additionally, our cohort consisted of 44.3% (436) females, and to date, is one of the largest cohorts of females used to evaluate COPD mortality. We used an easily identifiable IC/TLC cut-off of 25%, which has previously been validated.<sup>7</sup>

**Table 4** IC/TLC ratio in levels

Variable	HR	95% CI	P-value
IC/TLC levels			
>35% to $\leq 45\%$ vs >45%	1.76	1.07–2.89	0.025
>25% to $\leq 35\%$ vs >45%	2.82	1.76–4.53	<0.0001
$\leq 25\%$ vs >45%	5.23	3.28–8.35	<0.0001

**Abbreviations:** CI, confidence interval; HR, hazard ratio; IC, inspiratory capacity; TLC, total lung capacity.

The study does have limitations. It is a PF test-based study, assumptions about the patients' clinical phenotype were made on the basis of PF data, and no smoking history or radiological data were available. We did not evaluate or compare the BODE index or 6MWT. On the other hand, we did evaluate other well-defined variables including age, BMI, and FEV<sub>1</sub> in the analysis. We did not have PaO<sub>2</sub> values, therefore could not evaluate/correlate the degree of hypoxemia and its role in survival. The study inclusion criteria required a DLCO for the patient to be included in the analysis. In doing so, we eliminated patients who may have obstructive disease secondary to asthma, but undoubtedly removed many patients with COPD. We did not evaluate specific cause of death as previous studies have done, which prevented us from excluding patients that died from nonrespiratory events.

Our study demonstrates that the IC/TLC ratio  $\leq 25\%$  is strongly related to risk of death in an emphysematous phenotype of COPD patients. When compared to FEV<sub>1</sub> and other previously accepted variables, IC/TLC was a better predictor of survival in both univariate and multivariate analysis. Specifically, we found FEV<sub>1</sub> to be weakly associated with survival. When using patients with moderate severity as the reference group, those patients with mild disease were noted to have improved survival. Patients with severe and very severe disease did not have a statistically significant difference in mortality when compared to those individuals with moderately severe disease.

We believe that the reduced IC/TLC ratio, reflective of static lung hyperinflation, plays an important role in patients with an emphysematous phenotype of COPD. As hyperinflation progresses, patients experience increasing dyspnea and reduced exercise capacity. Dynamic lung hyperinflation is associated

with increasing end-expiratory lung volumes, which is associated with airflow limitation and loss of elastic recoil. In COPD, emphysematous changes in the lung are secondary to destruction of the elastic tissue in the lung parenchyma. As the lung parenchyma loses its elasticity, lung recoil is reduced, resulting in a compensatory increase in functional reserve capacity (FRC); as the FRC increases, the IC is reduced.<sup>49</sup> Therefore, in patients with COPD, the relationship between IC and TLC gradually declines as static lung hyperinflation increases. We found that the IC/TLC ratio strongly correlates with risk of death. In addition to risk of death, static lung hyperinflation has been reported to correlate with exercise capacity and cardiac performance in patients with COPD, thus adding to the clinical use of the IC/TLC ratio.

Previous studies of COPD patients often refer to the FEV<sub>1</sub> and its rate of decline to define treatment success or failure. Current treatment guidelines are based on the GOLD-defined FEV<sub>1</sub>, an endpoint that we found to have little correlation with survival. We believe that the IC/TLC ratio may be a more relevant variable for such analysis, possibly arguing for further studies.

In conclusion, a significant number of COPD patients have PF tests that include measurement of lung volumes. The IC/TLC ratio, like the BODE index, has demonstrated a correlation with COPD survival, is easy to obtain, and should be considered in the assessment of patients with an emphysematous phenotype of COPD.

## Disclosure

The authors report no conflicts of interest in this work.

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